



Contact for further information:  
Dr Katherine Boyd  
klb@ctu.mrc.ac.uk

# The Prevalence of Darunavir Associated Mutations in PI-naive and PI-experienced HIV-1 Infected Children in the UK

Katherine Boyd<sup>1</sup>, A. Sarah Walker<sup>1</sup>, David Dunn<sup>1</sup>, Ali Judd<sup>1</sup>, Deenan Pillay<sup>2</sup>, Esse Menson<sup>3</sup>, Gareth Tudor-Williams<sup>4</sup>, and Diana M. Gibb<sup>1</sup>

on behalf of the Collaborative HIV Paediatric Study (CHIPS) and the UK Collaborative Group on HIV Drug Resistance

<sup>1</sup> MRC Clinical Trials Unit, London, UK; <sup>2</sup> University College, London, UK; <sup>3</sup> St Thomas' NHS Trust, London, UK; <sup>4</sup> Imperial College, London, UK



Funding acknowledgement: Registration fees for CROI 2010 for Katherine Boyd were provided by Tibotec, a division of Janssen Cilag Ltd.

## Abstract

### Background

The protease inhibitor (PI) darunavir, boosted by ritonavir (DRV/r), is virologically effective and well tolerated in adults. Although co-formulated lopinavir (LPV/r) is currently the first-line PI for HIV-1 infected children in the UK, DRV/r has potential utility as once daily first- or second-line PI after previous PI failure. Identifying the prevalence of DRV/r resistance associated mutations (RAMs) in children is important for determining its clinical utility.

### Methods

Data during 1998-2007 combine that from the Collaborative HIV Paediatric Study (CHIPS, a cohort of ~95% reported HIV-1 infected children in UK/Ireland since 1996), and the UK HIV Drug Resistance Database. DRV RAMs were identified from the 2008 IAS mutations list (V111, V321, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V) with additional mutations (I47A, G73S/T/C, I84A/C, V82F) from the Stanford database. The prevalence of RAMs was estimated in (i) PI-naive children, using the first PI-naive test, and (ii) PI-experienced children, using cumulative resistance at the last test on a PI. Associations between the type and the duration of PI exposure and the area under the viraemia curve since the start of PI with the number of RAMs was analysed using multivariate Poisson regression. Susceptibility to DRV/r was defined using the Stanford algorithm.

### Results

344 children had a PI-naive resistance test. 14/344 (3%) had a single RAM (2 V111, 2 V321, 1 I47A, 7 I50V, 1 G73S, 1 L89V); none had multiple RAMs. 10 (83%) were non-B subtype virus. 156 children had a resistance test on PI at a median (IQR) 2.6 (1.2-5.0) years on PI; 55 (35%) had taken LPV/r as their only PI. 21(13%) had one RAM, 5 (3%) had 2, and 3 (2%) had 3. In a multivariate model, a higher number of DRV RAMs was independently associated with increased time on PI (p=0.04), larger area under the viraemia curve since the start of PI (p=0.01), and any exposure to a PI other than LPV/r (p=0.02 vs. LPV/r only). However, only 3 (2%) PI-experienced children had intermediate level resistance to DRV/r using Stanford.

### Conclusions

PI-naive children in the UK, and those whose only prior PI is LPV/r, have little DRV/r resistance, although the number of DRV RAMs increases slightly with an increased time and increased viraemia on PI. Few PI-experienced children have more than one DRV RAM and susceptibility to DRV/r is high. This suggests that once daily DRV/r may have utility both as a second PI as well as an alternative first PI, particularly if it can be co-formulated with a PI booster.

## Introduction

Darunavir, boosted by ritonavir (DRV/r), has been shown to have significant activity against both wild-type and multidrug-resistant HIV-1 strains and to be virologically effective and generally well tolerated in children.

- Currently, Lopinavir (LPV/r) is the preferred first PI in UK children and is licensed for all ages and weights in both tablet and syrup formulations.
- DRV/r is currently licensed in children aged 6+ years (twice-daily tablet). Trials of a suspension in 3-6 year olds, and once-daily administration across all ages, are ongoing.

### Resistance:

- The presence of ≥3 DRV resistance-associated mutations (RAMs) at baseline was associated with a diminished virological response to DRV/r in the POWER [1] and DUET [2] studies in adults.

- In previous studies of resistance in adults, over 90% harboured <3 DRV RAMs and over two thirds harboured none.

### Rationale:

- In the future, DRV/r may be of more use in children both as first PI or as second PI after previous failure on PI.
- Therefore, identifying the prevalence of resistance mutations both in PI-naive and PI experienced children is important for identifying clinical utility of DRV/r.

## Methods

### Data:

CHIPS is a multicentre cohort of HIV-infected children under care in 63 hospitals in the UK and Ireland since 1996. It is a collaboration between the clinical centres that care for HIV infected children, the National Study of HIV in Pregnancy and Childhood (NSHPC) at the Institute of Child Health, and the Medical Research Council (MRC) Clinical Trials Unit. The main objectives of CHIPS are to describe clinical, laboratory and treatment data for these children, and to describe the use of paediatric HIV services.

The UK HIV Drug Resistance Database is a central repository for resistance tests performed as part of routine clinical care throughout the U. Most of these (around 90%) are in the form of viral gene sequences. The Database is overseen by the UK Collaborative Group on HIV Drug Resistance.

### Mutations:

DRV resistance associated mutations are identified from the IAS 2008 Mutations list and the Stanford database.

<b>IAS 2008:</b>	V111, V321, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V
<b>Stanford database (additional mutations):</b>	I47A, G73S/T/C, I84A/C
<b>Other:</b>	V82F (Potential cross resistance)

In addition, V82A has been linked to improved response to DRV/r in adults with multiple DRV RAMs [3].

### PI naive children:

**Objective:** Estimate the prevalence of DRV resistance-associated mutations in PI-naive children in order to assess the potential use of DRV/r a first PI.

We will consider the first resistance test in children prior to starting a PI.

### PI experienced children:

**Objective:** Estimate the prevalence of DRV resistance-associated mutations in children when they might switch to a second PI due to failure or other reasons in order to evaluate the potential use of DRV/r after previous PI failure.

We will consider cumulative resistance at the last resistance test on PI (excluding all tests after starting DRV/r).

Multivariate linear regression will be used to examine associations between baseline demographics, time on PI (in years, time averaged), area under the viraemia curve, and type of PI. Susceptibility to DRV/r will be assessed using the Stanford database algorithm.

## Demographics

We use data from CHIPS and tests from the UK HIV Drug Resistance database to the end of December 2007. There are 1485 children in CHIPS in the UK between 1998-2007, of whom 1120 (75%) took HAART during the same period. Of these 559 (50%) took a PI including 406 (73%) who took LPV/r, 285 (51%) who took Nelfinavir (NFV), and 10 (2%) who took DRV/r.

Table 1: Demographics of children [Data are N (%) unless indicated]

	First resistance test while PI naive, N = 344	Last resistance test on PI, N = 156
Sex	Female 184 (53)	76 (49)
Ethnicity	Black African 283 (83)	116 (75)
	White 22 (6)	20 (13)
	Other 35 (11)	19 (12)
Born abroad	182 (53)	60 (38)
Med (IQR) age at presentation (yrs)	3.1 (0.5-7.8)	1.6 (0.2-5.3)
CDC stage C at presentation	29 (8)	20 (13)
Med (IQR) HIV-RNA at presentation (c/ml)	106,682 (25,600-424,410)	222,000 (73,784-529,321)
Med (IQR) CD4% at presentation	20 (13-28)	18 (10-29)
Subtype	C 172 (55)	58 (42)
	A 63 (20)	31 (23)
	B 22 (7)	19 (14)
	Other 56 (18)	30 (22)
Med (IQR) age at resistance test	8.1 (4.3-12.0)	11.2 (6.6-13.7)
CDC stage C at resistance test	71 (21)	73 (48)
Med (IQR) HIV-RNA at resistance test	25,000 (4,755-113,394)	11,998 (3,203-39,800)
Med (IQR) CD4% at resistance test	20 (14-28)	21 (12-30)

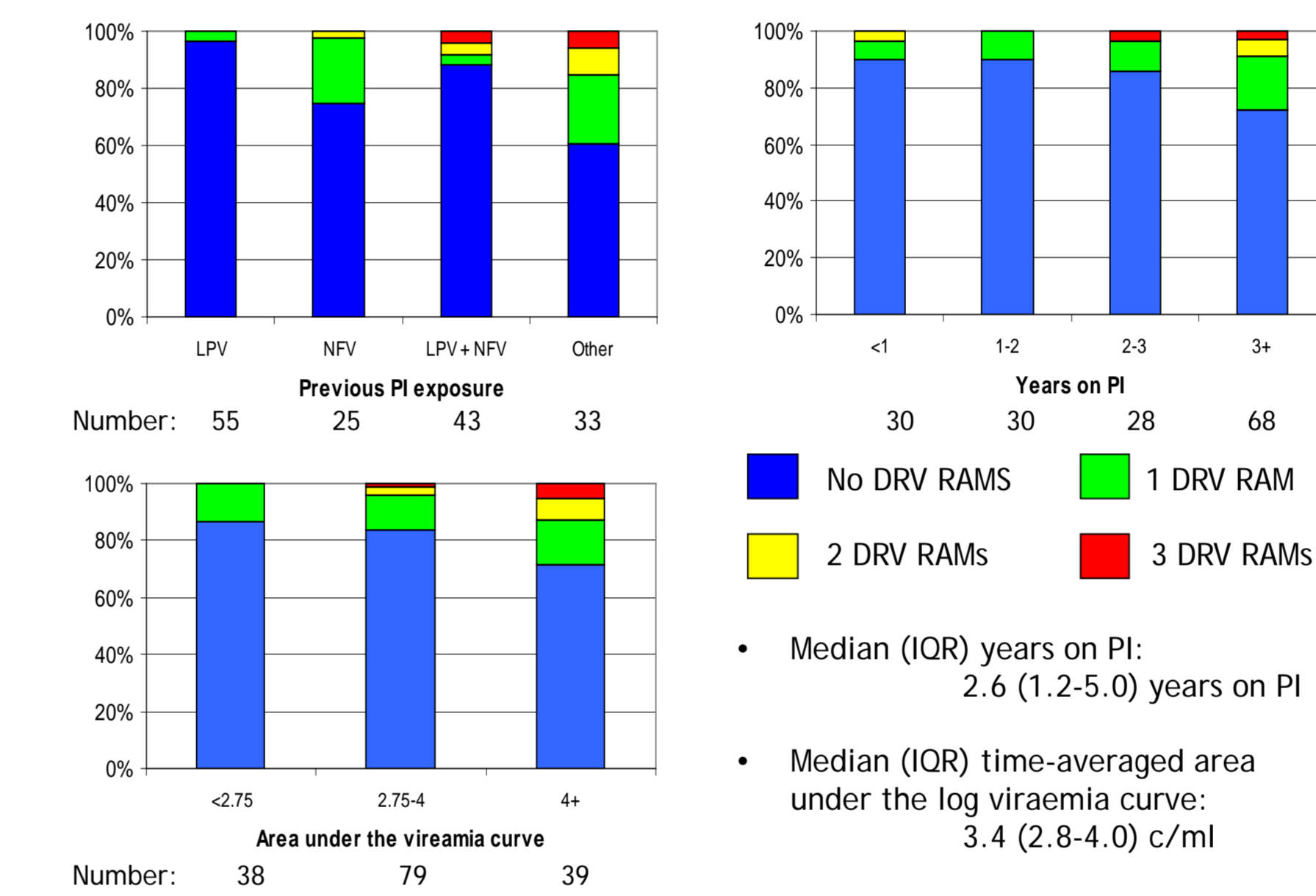
## PI naive children

- 1320 UK children in CHIPS were PI-naive at some point between 1998 and 2007, of whom 344 (26%) had a PI-naive resistance test.
- 12 (3%) children had IAS DRV RAMs. 2 children had V111 (1 subtype C, 1 unclassified), 2 had V321 (1 A, 1 D), 7 had I50V (2 B, 2 A, 2 G, 1 unclassified), and 1 had the L89V mutation (G).
- In addition - 1 child had I47A (unclassified) and 1 had G73S (C) - mutations from the Stanford database.
- 1 child had the V82A mutation.

## PI experienced children

- 595 UK children in CHIPS started a PI-containing regimen pre-2007
- There are 156 children with resistance tests while on a PI.
- 21(13%) had one DRV RAM, 5 (3%) had 2, and 3 (2%) had 3.

Figure 1: Association of prior PI use and the number of DRV RAMs



- Median (IQR) years on PI: 2.6 (1.2-5.0) years on PI
- Median (IQR) time-averaged area under the log viraemia curve: 3.4 (2.8-4.0) c/ml

Table 2: DRV RAMs present in children failing a PI regimen

Mutation	Number (%)	Mutation	Number (%)
V111	2 (1)	I47A	0 (0)
V321	1 (1)	G73S	0 (0)
L33F	6 (4)	G73T	0 (0)
I47V	1 (1)	G73C	4 (3)
I50V	5 (3)	I84A	0 (0)
I54L	3 (2)	I84C	1 (1)
I54M	0 (0)	I84V	6 (4)
T74P	1 (1)	L89V	5 (3)
L76V	5 (3)	V82F	3 (2)

Note: 7 (4%) have the V82A mutation, 1 of whom has 3 DRV RAMs.

Table 3: Association of PI use with the number of DRV RAMs from Poisson model

Factor*	Univariate IRR	(p-val)	Multivariate IRR	(p-val)
Years on PI (+ 1 yr)	1.24	(<0.001)	1.14	(0.04)
Prior use of PI other than LPV/r	10.35	(0.001)	6.15	(0.02)
Area under the viraemia curve (+1)	1.93	(0.001)	1.78	(0.01)

\* No other baseline factors were significant with p>0.1

Table 4: Susceptibility to DRV/r using the Stanford database in children failing a PI regimen, N (%)

Years on PI	Low level resistance	Intermediate resistance
<1 year	0 (0)	1 (3)
1-<2 years	2 (7)	0 (0)
2-<3 years	1 (4)	1 (4)
3+ years	10 (15)	1 (1)

Previous PI exposure	Low level resistance	Intermediate resistance
LPV	1 (2)	0 (0)
NFV	2 (8)	1 (4)
LPV + NFV	1 (2)	1 (2)
Other	9 (27)	1 (3)

Time averaged area under the viraemia curve	Low level resistance	Intermediate resistance
<2.75	2 (5)	0 (0)
2.75-4	4 (5)	2 (3)
4+	7 (18)	1 (3)

## Summary and Conclusions

- DRV RAMs are very rare in PI-naive children.
- The prevalence of DRV RAMs is low in those whose only PI exposure is LPV/r. It is higher in those with exposure to other PIs other than LPV (likely due to failure).
- At the last test on PI only 3 children had 3 DRV RAMs.
- There is an increase in resistance with >2 years PI exposure and increase viraemia.
- Overall, results suggest that DRV/r is of use as both a first PI and an alternative second PI as resistance is low.
- We could consider specific analyses looking at the relationship between LPV/r exposure and DRV RAMs using random effects modelling although RAM rates are low.
- ATV/r is only licensed OD for children age 6+ years (weighing ≥25kg if ART-exp). It may also be of interest as a alternative first, or as a second, PI.

### References:

- De Meyer, S. et al. 2008. Resistance profile of darunavir: combined 24-week results from the POWER trials. AIDS Res Hum Retroviruses 24: 379-388.
- De Meyer, S. et al. 2008. Phenotypic and genotypic determinants of resistance to darunavir: analysis of data from treatment experienced patients in POWER 1, 2, 3 and DUET-1 and 2. Antivir Ther 13: Suppl3:A33.
- De Meyer, S. et al. 2009. Confirmation of the negative impact of protease mutations I47V, I54M, T74P, and I84V and the positive impact of protease mutation V82A on virological response to darunavir/ritonavir. Poster 126, XVIII International HIV Drug Resistance Workshop.

**UK COLLABORATIVE GROUP ON HIV DRUG RESISTANCE Funding:** The UK HIV Drug Resistance Database is partly funded by the Department of Health: the views expressed in the publication are those of the authors and not necessarily those of the Department of Health. Additional financial support is provided by Boehringer Ingelheim: Bristol-Myers Squibb; Gilead; Roche; Tibotec, a division of Janssen-Cilag Ltd. **Steering Committee:** Jane Anderson, Homerton University Hospital, London; David Asboe and Anton Pozniak, Chelsea & Westminster Hospital, London; Sheila Burns, Royal Infirmary of Edinburgh; Sheila Cameron, Gartnavel General Hospital, Glasgow; Patricia Cane, Health Protection Agency, Porton Down; Ian Chrystie, Guy's and St. Thomas' NHS Foundation Trust, London; Duncan Churchill, Brighton and Sussex University Hospitals NHS Trust; Duncan Clark, St Bartholomew's and The London NHS Trust; Valerie Delpech and Deenan Pillay, Health Protection Agency, Centre for Infections, London; Linda Lazarus, Expert Advisory Group on AIDS Secretariat, Health Protection Agency, London; David Dunn, Esther Fearnhill, Hannah Castro and Kholoud Porter, MRC Clinical Trials Unit, London; Philippa Easterbrook and Mark Zuckerman, King's College Hospital, London; Anna Maria Geretti, Royal Free NHS Trust, London; Paul Kellam, Deenan Pillay, Andrew Phillips and Caroline Sabin, Royal Free and University College Medical School, London; David Goldberg, Health Protection Scotland, Glasgow; Mark Gompels, Southmead Hospital, Bristol; Antony Hale, Leeds Teaching Hospitals NHS Trust; Steve Kaye, St. Mary's Hospital, London; Svilen Konov, Community Advisory Board; Andrew Leigh-Brown, University of Edinburgh; Nicola Mackie, St. Mary's Hospital, London; Chloe Orkin, St. Bartholomew's Hospital, London; Erasmus Smit, Health Protection Agency, Birmingham Heartlands Hospital; Peter Tilston, Manchester Royal Infirmary; Ian Williams, Mortimer Market Centre, London; Hongyi Zhang, Addenbrooke's Hospital, Cambridge **Participating laboratories:** Addenbrooke's Hospital, Cambridge (Hongyi Zhang); Department of Virology, St Bartholomew's and The London NHS Trust (Duncan Clark, Ines Ushiro-Lumb, Tony Oliver, David Bibby); Belfast Health and Social Care Trust (Suzanne Mitchell); HPA Birmingham Public Health Laboratory (Erasmus Smit); Chelsea and Westminster Hospital, London (Adrian Wildfire); Dulwich Hospital, London (Melvyn Smith); Royal Infirmary of Edinburgh (Jill Shepherd); West of Scotland Specialist Virology Lab Gartnavel, Glasgow (Ailsa MacLean); Guy's and St. Thomas' NHS Foundation Trust, London (Ian Chrystie); Leeds Teaching Hospitals NHS Trust (Diane Bennett); Specialist Virology Centre, Liverpool (Mark Hopkins) and Manchester (Peter Tilston); Department of Virology at Royal Free Hospital, London (Clare Booth, Ana Garcia-Diaz); St Mary's Hospital, London (Steve Kaye); University College London Hospitals (Stuart Kirk)

**CHIPS Funding:** NSHPC is funded by the Health Protection Agency, and has also received support from the UK Department of Health and the Medical Research Council. CHIPS is funded by the Department of Health and in the past received additional support from Bristol-Myers Squibb, Boehringer Ingelheim, GlaxoSmithKline, Roche, Abbott, and Gilead. **Committees and participants** (in alphabetical order): CHIPS Steering Committee: KL Boyd, K Butler, K Doerholt, S Donaghy, DT Dunn, DM Gibb, A Judd, EGH Lyall, J Masters, E Menson, B Murphy, V Novelli, C Peckham, A Riordan, M Sharland, D Shingadia, PA Tookey, G Tudor-Williams; MRC Clinical Trials Unit: KL Boyd, DT Dunn, L Harper, DM Gibb, D Johnson, A Judd, B Murphy; National Study of HIV in Pregnancy & Childhood, Institute of Child Health: J Masters, C Peckham, PA Tookey. **We thank the staff, families & children from the following hospitals who participate in CHIPS** (in alphabetical order): Republic of Ireland: Our Lady's Children's Hospital Crumlin, Dublin; K Butler, A Walsh. UK: Birmingham Heartlands Hospital, Birmingham; Y Heath, J Sillis; Blackpool Victoria Hospital, Blackpool; N Laycock; Bristol Royal Hospital for Children, Bristol; A Finn, A Foot, L Hutchison; Central Middlesex Hospital, London; M Le Provost, A Williams; Chase Farm Hospital, Middlesex; Chelsea and Westminster Hospital, London; D Hamadache, EGH Lyall, P Seery; Ealing Hospital, Middlesex; V Shah, K Sloper; Glasgow Royal Hospital for Sick Children, Glasgow; C Doherty, R Hague; Great Ormond St Hospital for Children, London; M Clapson, S Fasolo, J Flynn, DM Gibb, N Klein, K Moshal, V Novelli, D Shingadia; Hillingdon Hospital, London; Homerton University Hospital, London; D Gurtin; John Radcliffe Hospital, Oxford; A Pollard, S Segal; King's College Hospital, London; C Ball, S Hawkins, D Nayagam; Leeds General Infirmary, Leeds; P Chetcuti; Leicester Royal Infirmary, Leicester; M Green, J Houghton; Luton and Dunstable Hospital, Luton; M Connan, M Eisenhut; Mayday University Hospital, Croydon; J Bayerstock, C Waruiru; Newham General Hospital, London; C Donoghue, E Cooper, S Liebeschuetz, S Wong; Nineveh Hospital and Medical School, Dundee; T Lornie; North Manchester General Hospital, Manchester; C Murphy, T Tan; North Middlesex Hospital, London; J Daniels, EGH Lyall, B Sampson-Davis; Northampton General Hospital, Northampton; F Thompson; Northwick Park Hospital, Middlesex; M Le Provost, A Williams; Nottingham City Hospital, Nottingham; D Curnock, A Smyth, M Yanney; Queen Elizabeth Hospital, Woolwich; W Faulknaill, S Mitchell; Royal Belfast Hospital for Sick Children, Belfast; S Christie; Royal Edinburgh Hospital for Sick Children, Edinburgh; J Mok; Royal Free Hospital, London; S McKenna, V Van Someren; Royal Liverpool Children's Hospital, Liverpool; C Benson, A Riordan; Royal London Hospital, London; B Ramaboea, A Riddell; Royal Preston Hospital, Preston; AN Campbell; Sheffield Children's Hospital, Sheffield; J Hobbs, F Shackley; St George's Hospital, London; R Chakraborty, S Donaghy, R Fluke, M Sharland, S Storey, C Wells; St Mary's Hospital, London; D Hamadache, C Hanley, EGH Lyall, G Tudor-Williams, C Walsh, S Walters; St Thomas' Hospital, London; R Cross, G Du Mont, E Menson; University Hospital Lewisham, London; D Scott, J Stroobant; University Hospital of North Staffordshire, Stoke On Trent; P McMaster; University Hospital of Wales, Cardiff; B O' Hare; Wexham Park, Slough; R Jones; Whips Cross Hospital, London; K Gardiner; Whittington Hospital, London.